Methyl 2,3,6-tri-O-Benzoyl-4-O-(tert-butyldimethylsilyl)-ß-d-galactopyranoside

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Short Note

Methyl 2,3,6-tri-*O*-Benzoyl-4-*O*-(tert-butyldimethylsilyl)-β-D-galactopyranoside

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Abstract: Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(tert-butyldimethylsilyl)-β-D-galactopyranoside was synthesized in 47% yield by the silylation of a partially benzoylated galactose derivative, prepared from methyl β-D-galactopyranoside. The product was characterized by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectrometry.

Keywords: galactose; monosaccharide; silylation; benzoylation; NMR

1. Introduction

Galactose is a monosaccharide found in many glycans that cover a wide range of applications in biomedicine and in the bioeconomy [1,2]. Galectin-3, for example, plays a crucial role in many physiological processes, including cancer development and inflammation, by its recognition of β-galactoside derivatives. Thus, the synthesis of novel β-galactoside compounds as a means of inhibiting galectin-3 has been a growing area of research in recent years [3,4]. α-Galactosides are also important, such as α-galactosylceramides, which have been shown to be ligands for natural killer T-cells and to possess potent anti-tumour activity [5].

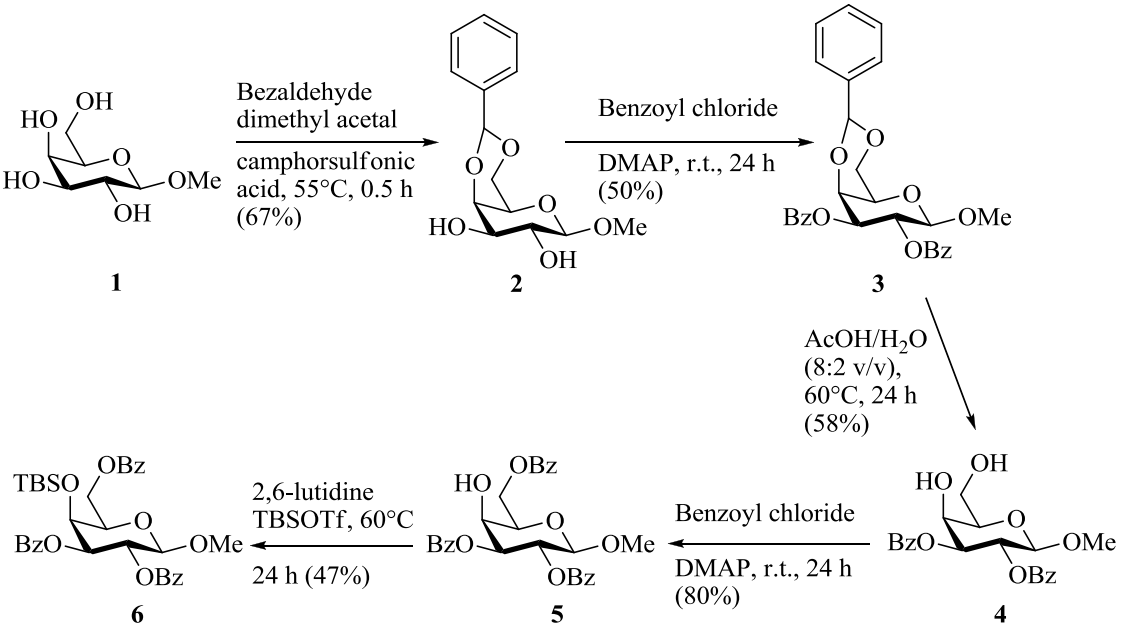
The conversion of β-glycosides to α-glycosides by anomerisation has been an interest in our group [6–9]. In the case of bioactive compounds containing a galactose monomer, improvements in the anomerisation reactions of galactose mono- and disaccharides could potentially lead to more efficient syntheses of such compounds from a wider range of starting materials. For this reason we have been exploring factors affecting reactivity to anomerisation, including the role of protecting groups, which includes the impact of silyl derivatives. In this context, we have prepared the title compound and provide the record of its synthesis and analytical data herein.

2. Results and Discussion

Methyl β-D-galactopyranoside (**1**) was initially protected at the 4- and 6-position (Scheme 1). This was carried out using benzaldehyde dimethyl acetal [10], forming methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**2**) as a white solid (67%). This product was then benzoylated at the 2- and 3-positions using benzoyl chloride in the presence of pyridine [11] to give methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-β-D-galactopyranoside (**3**) as a white solid (50%). The benzylidene group was then removed using acetic acid in water (8:2 *v*/*v*) to give methyl 2,3-di-*O*-benzoyl-β-D-galactopyranoside (**4**) as a white solid (58%) [12]. Next, regioselective benzoylation gave methyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside (**5**) as an off-white solid (80%). In the final step, compound **5** was silylated at the 5-position using tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) [13] to afford the title compound methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(tert-butyldimethylsilyl)-β-D-galactopyranoside (**6**) as a white foam (47%). ^{1}H-, ^{13}C- and gCOSY NMR spectra along with IR and mass spectrometry supported

the structural assignment and gave a qualitative indication of its purity. The NMR spectra obtained for (**6**) are provided as Supplementary Materials.

All reactions (with the exception of the deprotection step) were carried out under an inert nitrogen atmosphere using anhydrous solvents to ensure thoroughly dry reaction conditions. All reactions were monitored by TLC.



Scheme 1. Synthesis of **6** from methyl β-D-galactopyranoside.

3. Materials and Methods

3.1. General Information

All analytical data for previously reported compounds (**2–5**) was found to be in accordance with data reported previously in the literature, and citations are provided. All reagents used were obtained from commercial sources and used without further purification. TLC experiments were performed using aluminium sheets pre-coated with silica gel 60 (HF_{254}, E. Merck, Darmstadt, Germany). NMR experiments were carried out in $CDCl_3$ using a 500 MHz spectrometer (Varian Ltd., CA, Palo Alto, USA), with the chemical shifts reported relative to internal Me_4Si. NMR spectra were analysed using MestReNova software (version 11, Mestrelab Research, Santiago de Compostela, Spain). The IR spectrum was obtained using FTIR Spectrometer (Perkin Elmer Spectrum 100, Shelton, CT, USA). A mass spectrum was obtained using a Waters LCT Premier XE Spectrometer. Chromatography was performed with silica gel 60 (Sigma Aldrich, Wicklow, Ireland). Petroleum ether was the fraction with boiling point 40–60 °C.

3.2. Methyl 4,6-O-Benzylidene-β-D-galactopyranoside (**2**)

Methyl β-D-galactopyranoside (**1**) (2.01 g, 10.4 mmol) was dissolved in dry acetonitrile (35 mL) under a nitrogen atmosphere. Benzaldehyde dimethyl acetal (3.11 mL, 20.8 mmol) was added, followed by camphorsulfonic acid (480 mg, 2.08 mmol). The reaction mixture was stirred under nitrogen for 30 min at 55 °C. The reaction was quenched with triethylamine (0.3 mL). The residue was concentrated to dryness under reduced pressure and then recrystallised from ethyl acetate (EtOAc), to give 1.95 g (67%) of compound **2** as a white solid. The ^{1}H-NMR data of **2** was in accordance with data reported previously in the literature [10].

*3.3. Methyl 4,6-O-Benzylidene-2,3-*di*-O-benzoyl-β-D-galactopyranoside* (**3**)

Compound **2** (1.95 g, 6.88 mmol) was dissolved in dry pyridine (10 mL) under nitrogen. 4-Dimethylaminopyridine (10 g) was added next, and the solution was then cooled to 0 °C. Benzoyl chloride (4.81 mL, 41.41 mmol) was added slowly, and the mixture was left at room temperature for 24 h. The mixture was then diluted with dichloromethane, washed with hydrochloric acid (to react with excess pyridine), dried over Na_2SO_4 and then concentrated to dryness under reduced pressure. Column chromatography, using a mixture of petroleum ether–EtOAc (2:1) as the mobile phase afforded 1.68 g (50%) of compound **3** as a white solid. ^{1}H-NMR spectroscopic data for the product was in agreement with data reported previously [14].

*3.4. Methyl 2,3-*di-*O-Benzoyl-β-D-galactopyranoside* (**4**)

Compound **3** (1.68 g, 3.42 mmol) was dissolved in AcOH–H_2O (20 mL, 8:2 *v*/*v*), heated to 60 °C and left to react for 24 h. The mixture was then diluted with EtOAc and washed through with $NaHCO_3$ (2 × 15 mL) and brine (15 mL). Column chromatography on silica gel using petroleum ether–EtOAc (1:2) as the mobile phase afforded 805 mg (58%) of compound **4** as a white solid. ^{1}H-NMR spectroscopic data for the product was in agreement with data reported previously [15].

*3.5. Methyl 2,3,6-*tri-*O-Benzoyl-β-D-galactopyranoside* (**5**)

Compound **4** (805 mg, 2.00 mmol) was selectively benzoylated at the 6-position using benzoyl chloride (0.348 mL, 3.00 mmol) and the same method outlined previously. Column chromatography on silica gel using petroleum ether–EtOAc (3:1) as the mobile phase gave 807 mg (80%) of compound **5** as an off-white solid. ^{1}H-NMR spectroscopic data for the product was in agreement with data reported previously [16].

*3.6. Methyl 2,3,6-*tri-*O-Benzoyl-4-O-(tert-butyldimethylsilyl)-β-D-galactopyranoside* (**6**)

Methyl 2,3,6-tri-O-benzoyl-β-D-galactopyranoside (**5)** (807 mg, 1.59 mmol) was dissolved in dry pyridine (10 mL) under nitrogen. TBSOTf (0.730 mL, 3.18 mmol) and 2,6-lutidine (0.370 mL, 3.18 mmol) were added via syringe at 0 °C. The reaction mixture was then stirred under nitrogen for 24 h at 60 °C. The solution was washed with excess 1 M HCl (2 × 25 mL), dried over Na_2SO_4 and then concentrated to dryness under reduced pressure. Column chromatography using petroleum ether–EtOAc (4:1) as the mobile phase afforded the title compound **6** (468 mg, 47%) as a white foam; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.08–8.04 (m, 2H, aromatic H), 7.98–7.92 (m, 4H, aromatic H), 7.62–7.57 (m, 1H, aromatic H), 7.52–7.44 (m, 4H, aromatic H), 7.35 (m, 4H, aromatic H), 5.82 (dd, *J* = 10.5, 7.9 Hz, 1H, H-2), 5.24 (dd, *J* = 10.5, 2.8 Hz, 1H, H-3), 4.67 (d, *J* = 7.9 Hz, 1H, H-1), 4.63 (dd, *J* = 11.1, 6.5 Hz, 1H, H-6a), 4.46 (m, 1H, H-4), 4.42 (dd, *J* = 11.1, 6.7 Hz, 1H, H-6b), 4.05 (m, 1H, H-5), 3.55 (s, 3H), 0.96 (s, 9H), 0.01 (s, *J* = 2.9 Hz, 3H), −0.10 (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 166.60 (C=O), 166.35 (C=O), 165.68 (C=O), 133.55 (C-Ar), 133.42 (C-Ar), 133.20 (C-Ar), 130.03 (C-Ar), 129.85 (C-Ar), 129.83 (C-Ar), 129.80 (C-Ar), 129.36 (C-Ar), 128.67 (C-Ar), 128.57 (C-Ar), 128.45 (C-Ar), 102.29 (CH, C-1), 75.25 (CH, C-3), 72.90 (CH, C-5), 69.26 (CH, C-2), 68.55 (CH, C-4), 63.14 (CH_2, C-6), 56.78 (CH_3-O), 26.01 (TBS), 18.45 (TBS), −4.39 (TBS), −4.46 (TBS); FT-IR: 2931, 2857, 1720, 1602, 1451, 1264, 1069, 832, 775, 706 cm^{-1}; HRMS (TOF MS ES+) *m*/z: [M + Na]$^+$ Calc. for $C_{34}H_{40}O_9SiNa^+$: 643.2334. Found: 643.2397.

Supplementary Materials: ^{1}H- and ^{13}C-NMR spectra of compound **6** are available online.

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Conflicts of Interest: The authors declare no conflict of interest.

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